REMARKS

In the pending Office Action, the Examiner rejected pending claims 1-14. Upon entry of the present amendment, claims 1-3 and 14-23 are pending in this application. Claims 1-3 and 14 have been amended and claims 15-23 have been added. Support for amended claims and new claims can be found in the claims as originally filed. Therefore, no new matter has been added

The Examiner's rejections and objections are addressed in turn as set forth in the Office Action.

REJECTION UNDER 35 U.S.C §112, FIRST PARAGRAPH

Claims 1-14 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. It is the Examiner's opinion that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner contends that the claims are not enabled because there is no evidence that Applicants' claimed invention produces a therapeutic benefit. Further, the Examiner has asserted that one skilled in the art could not, without undue experimentation, make and use the claimed invention based on the disclosure in the application and the level of information known in the art.

Applicants traverse the Examiner's §112 rejection on the following three grounds: (1) the §112, first paragraph, rejection is improperly made; (2) the "how to use" requirement of §112 has been met; and (3) undue experimentation is not necessary for the skilled artisan to practice the claimed invention. These grounds for traversal are discussed in detail as set forth below.

I. The § 112 Rejection Is Improper

In the first instance, Applicants submit that the § 112, first paragraph rejection is improper. On page 3 of the Office Action, the Examiner states that "it is unclear if the enhancement of the immune response would be sufficient to result in a therapeutically effective result in humans or animals suffering from naturally occurring cancers." Where, as here, the Examiner has questioned the therapeutic efficacy or benefit, the rejection is properly the subject of a § 101 utility rejection

(with a concurrent § 112, first paragraph, rejection) on the basis that the claimed invention lacks a credible utility. *See* M.P.E.P. §§ 706.03(a)(1) and 2107. There is no § 101 rejection here.

To uphold a utility-based § 112, first paragraph, rejection, a case must represent one of those rare instances that meets the stringent criterion of being "totally incapable of achieving a useful result." *See Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555 (Fed. Cir. 1992). (M.P.E.P. § 2107). The only rare instances in which the Federal courts have found a lack of patentable utility were where, "based upon the factual record of the case, it was clear that the invention *could and did not work* as the inventor claimed it did." M.P.E.P. § 2107 (emphasis added). These rare cases have been ones in which the applicant either (a) failed to disclose any utility for the invention, or (b) asserted a utility that could be true only "if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." M.P.E.P. § 2107.01. Neither is true here.

In conformity with the Guidelines, Applicants asserted in the specification that the invention has multiple utilities, including use as an inhibitor of tumor-induced immunosuppression (*see* specification at p. 10, lines 2-5) and use as an enhancer of immunotherapy (*see* specification at p. 10, lines 9-13) .

The Utility Guidelines state that "data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition, or process." M.P.E.P. § 2107.02(a).[1/] Applicants have provided evidence of record both in the specification and in the enclosed Declaration establishing utility in animal models.

Accordingly, Applicants submit that the utility-based § 112, first paragraph, rejection was not properly made and should be withdrawn.

II. The "How to Use" Requirement of § 112 Rejection Is Improper

Applicants submit that the "how to use" requirement of § 112, first paragraph, has been satisfied. The "how to use" requirement of § 112, first paragraph, is satisfied if "the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of

[1/] Consistent with this standard, in no case has a Federal court required an Applicant to support an asserted utility with data from human clinical trials. M.P.E.P. § 2107.02(d).

administration are known and contemplated." *See* M.P.E.P. § 2164.01(c). Applicants' specification meets this requirement (discussed in detail below).

The Examiner's determination that the claims are not enabled fails to follow the procedures set forth in the M.P.E.P. M.P.E.P. § 2164.01(c) "How to Use the Claimed Invention" describes how a Patent Examiner must address issues of enablement:

> In contrast, when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use. If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention.

Applicants submit that the amended claims do not recite any requirement for providing a therapeutic benefit to a host. The claims recite methods for enhancing an anti-tumor response to immunotherapy or methods for counteracting tumor-induced immunosuppression. The Examiner acknowledges in the Office Action that Applicants have presented data demonstrating enhancement of the immune response, but then argues that "it is unclear if the enhancement of the immune response would be sufficient to result in a therapeutically effective result in humans or animals suffering from naturally occurring cancers." *See* Office Action at p. 3. Applicants submit that the claims as amended, do not require the therapeutic benefit cited by the Examiner. The claims require only that the anti-tumor immune response be enhanced and the Examiner has acknowledged that the data demonstrates that this requirement has been fulfilled.

III. Undue Experimentation is Not Necessary to Make or Use the Invention

A rejection under § 112, first paragraph, is proper only if one reasonably skilled in the art could not make or use the invention from the disclosures in the patent application coupled with information known in the art, without undue experimentation. *See United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988); *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). In determining whether there is sufficient evidence to support a *prima facie* case of lack of enablement, the Examiner has asserted that unpredictability in the art, the lack of a working example, and an insufficient amount of guidance from the applicants would have required a skilled artisan "to have

conducted undue and excessive experimentation in order to reduce the claimed invention to practice" (*see* Office Action at page 6). The specification and the Declaration submitted herein by Dr. Klaus Edvardsen, a scientist skilled in the art of tumor immunotherapy, provide *prima facie* evidence that at the time the application was filed, the specification would have taught one skilled in the art how to use the full scope of the claimed invention without undue experimentation. A holding of "undue experimentation" cannot stand.

The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. *See* MPEP 2164.03. The Declaration and the references cited therein indicate that the state of the art at the time the application was filed was sufficient to allow one skilled in the art to extrapolate the disclosed results of the claimed invention on an animal model and readily anticipate their use in all warm-blooded animals including humans. With regard to the use of immunotherapy in treating cancer, the teachings of the prior art indicated that immunotherapy was a known strategy which could result in therapeutic benefit and efficacy when administered to humans. In particular, the technique of tumor cell immuno-gene therapy was a well established approach that had been tested in clinical trials with effective results.

The Declarant cites the published results of a phase I/II clinical study by Osanto *et al.*, (Human Gene Therapy, 11(5): 739-50, 2000) in which human patients were vaccinated with melanoma cells that had been transfected *ex vivo* with the immunostimulatory cytokine gene, Interleukin-2 (IL-2). Osanto *et al.* demonstrated that in metastatic melanoma patients treated with IL-2 transfected tumor cells, T-cell infiltration and an anti-tumor inflammatory response was observed at metastatic sites. Two patients had experienced complete or partial regression of subcutaneous metastases. An additional seven patients had a protracted stabilization of soft-tissue metastases. In total, immune response could be detected in 67% of the 27 patients measured. The researchers concluded that the vaccination of human with allogeneic, gene-modified tumor cells had "therapeutic potential". Thus, the prior art at the time of the present invention provided sufficient evidence to demonstrate the effectiveness of tumor cell immuno-gene therapy. The immunotherapy strategy used by the Applicants was similar to that of Osanto *et al.* Tumor cell vaccines were

created by transfection with the immunostimulatory cytokines Interleukin-12 (IL-12) and Interleukin-18 (IL-18).

While the above evidence demonstrates that immuno-gene therapy of tumor cells had experienced some clinical success at the time the subject application was filed, it was recognized and acknowledged by the Declarant and others skilled in the art that the effectiveness of tumor cell immuno-gene therapy could be improved by counteracting the tumor-induced immunosuppression that is often observed with this therapy. It was demonstrated with high predictability that tumors were capable of inducing immunosuppression. Indeed, Gomez-Navarro *et al.* (European Journal of Cancer, 1999, Vol 35 (6): p874, cited at page 4 of the Office Action) suggested that "the presence of immunosuppressive factors in tumors suggest the need to complement any immunotherapy strategy with maneuvers explicitly addressing the intratumoral presence of inhibitors of the immune system response, a combined strategy which to our knowledge is yet to be tested."

Based on the need in the art to provide an improved method of immunotherapy to overcome the limitations due to tumor-induced immunosuppression, the Applicants provided a method of counteracting tumor-induced immunosuppression with a low dose of Combretastatin A4, prodrugs, or mixtures thereof in an amount effective to enhance an anti-tumor response. The Applicants also provided a method of modulating the immune responsiveness in a warm-blooded animal bearing a tumor and treated with immunotherapy by administering a low-dose of Combretastatin A4, prodrugs, or mixtures thereof. These methods constitute the full scope of what the Applicants regard as their claimed invention. The Applicants do not claim the use of a low dose of Combretastatin A4, prodrugs, or mixtures thereof as a method of treating cancer *per se*. Indeed, as the Declarant states, the Applicants discovered that a low dose of the prodrug Combretastatin A-4 Phosphate ("CA4P") is not effective in shutting down tumor-blood flow (*see* page 17 of specification). Since the cessation of tumor blood flow is the art-recognized mechanism by which a higher dose of CA4P controls tumor growth, the Applicants did not seek to demonstrate how to use a low dose CA4P as an anti-cancer agent, since this is not their claimed invention. The proper focus of examination inquiry is whether the claimed invention is enabled. In addressing whether the full scope of the enablement is sufficient to practice the claimed invention "without undue experimentation", the only relevant concern is whether there is a "reasonable correlation" between the scope of enablement and the scope of the claims. *See* MPEP 2164.08.

As the enclosed Declaration illustrates, a method of testing the ability of Combretastatin A-4, its prodrugs, and mixtures thereof to inhibit tumor-induced immunosuppression or enhance immune responsiveness is provided in the form of both *in vitro* data and *in vivo* animal data. The animal data demonstrates the effectiveness of Combretastatin A-4 in counteracting the tumor-induced immunosuppression observed in a tumor-bearing rat previously treated with immuno-gene therapy. Dr. Edvardsen submits that this rat model recapitulates the phenomena of tumor induced immunosuppression that is observed in both rats and humans, and that the rat model utilized in the specification is commonly recognized and accepted by practitioners in the art of immunotherapy as being reasonably correlative with the condition of tumor-induced immunosuppression that is observed in humans.

In the attached Declaration, the Declarant also addresses the article by Gura (Science, 1997, Vol. 278, pp. 1041-42), which the Examiner cites as evidence that cell and animal models are often not predictive with regard to the effectiveness for humans. As Dr. Edvardsen notes, the Gura reference refers specifically to the ability of animal models in predicting the efficacy of a candidate anti-cancer drug in killing tumor cells or counteracting cancer growth. The reference does not speak to the applicability of using animal tumor models to evaluate the effects of drugs in treating tumor-induced immunosuppression. Again, it is reiterated that Applicant's claimed invention encompasses the discovery that a low dose of CA4P is capable of counteracting tumor-induced immunosuppression and not tumor cell growth. Since the *in vitro* and *in vivo* model examples are recognized by those skilled in the art as being sufficiently correlative to claimed methods of use, the Applicants submit that these data constitute "working examples", which enable individuals skilled in the art of immunotherapy to practice the claimed invention without undue experimentation and with a reasonable chance of success.

In disclosing how to make the claimed invention and how to reduce the claimed invention to practice, the specification of the subject application meets the standard set forth in issued US patents with claims granted for use of immunotherapy, and in particular tumor cell immuno-gene therapy. For example, in US Patent No. 6,051,428 (issued on April 18, 2000), Fong *et al.* describe a method of producing an autologous tumor cell vaccine *ex vivo* by transducing the patients own tumor cells with the gene for the immunostimulatory cytokine, Interleukin-2 (IL-2). Fong *et al.* go on to describe how to make and use the subject invention. Examples 6, 10, and 27 describe *in vivo* antitumor experiments to determine the efficacy of the immunization on immune cell activity and

tumor growth *in vivo* by pretreatment of syngeneic non-tumor bearing C57B1/6j mice. In each case, the pretreatment consisted of an injection of IL-2 transduced murine hepatic tumor cell vaccine. The mice were subsequently challenged three weeks later by injection of replicating tumor cells. Tumor growth and splenocyte proliferation was evaluated following an additional 3 weeks of incubation.

In Example 21 and 22, experiments with experimental rats are described. The inventors evaluated the tumorogenicity of injected rat hepatoma tumor cells transduced with rat ICAM-1, an immunomodulatory compound, and evaluated the ability of prior exposure to ICAM-1-transduced tumor cells to protect against subsequent challenge with the untransduced rat tumor cells. Thus, in every *in vivo* model described, either rat or murine genes, tumor cells, and animal host were allogeneic as in the subject invention. No naturally derived tumor, either animal or human, was used in any experiment. Furthermore, the animals were subjected to treatment before the onset of disease, which is a less natural scenario than the one described in the subject application, where tumor-bearing animals are treated. Nevertheless, the US Patent Office found the experimental data disclosed in Fong *et al.* to be sufficiently enabling and supportive of claims for methods of treating cancer. The claims were allowed and the patent proceeded to issuance more than one year prior to the filing date of the subject application. When evaluating the anti-tumor efficacy of CA4P and immunotherapy, the subject application not only meets, but it exceeds the standard of enablement of an immunotherapy treatment set forth in the Fong *et al.* patent.

Accordingly, Applicants submit that undue experimentation is not be required by a skilled artisan in order to practice the claimed invention of modulating anti-tumor immune response. For all the foregoing reasons, Applicants respectfully submit that the rejection should be withdrawn because the pending claims are enabled.

REJECTION UNDER 35 U.S.C §112, SECOND PARAGRAPH

Claims 1-14 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, which Applicants regard as the invention. The Examiner considers the phrases "composition" and "substantial" in these claims to be unclear. In order to overcome this rejection, the amended claims and the new claims do not contain the phrases "composition" or "substantial". The claims specify a single compound, either

CA4 or a prodrug thereof, for use in the invention. Accordingly, Applicants respectfully request the withdrawal of this rejection.

CONCLUSION

In view of the aforementioned remarks and amendments, the Applicants believe that each of the pending claims is in condition for allowance. Reconsideration, withdrawal of the rejections, and passage of the case to issue is respectfully requested. A notice to this effect is earnestly solicited.

If, upon receipt and review of this amendment, the Examiner believes that the present application is not in condition for allowance and that changes can be suggested which would place the claims in allowable form, the Examiner is respectfully requested to call Applicants' undersigned counsel at the number provided below.

Respectfully submitted,

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